REMARKS

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 1-13 were pending in this application and were rejected on various grounds. Claim 5 have been amended to recite a functional limitation. Support for the functional limitation can be found in the Specification as filed, for example page 93. Claims 1-4 have been cancelled without prejudice or disclaimer for pursuit of their subject matter in latter continuation or divisional filings. The rejections to the presently pending claims are respectfully traversed.

The changes made to the Specification and Claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined.

Priority

Applicants acknowledge that the Examiner has granted the present application the priority date of **August 24, 2000**.

Specification

The disclosure was objected to by the Examiner as containing trademarks which were not capitalized and did not include the generic terminology. The specification has been amended to include these changes. The specification has also been amended to delete reference to embedded hyperlinks.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Claim Rejections — 35 U.S.C. § 101 and § 112, 1st Paragraph

The Examiner rejected Claims 1-13 as lacking either a specific and substantial asserted utility or a well established utility under 35 U.S.C. § 101. Claims 1-13 are also rejected under 35 U.S.C. § 112, first paragraph for lack of utility. According to the Examiner, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established

utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully disagree with and traverse these rejections.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." A utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the

facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Absolute predictability is not a requirement. Only after the Examiner has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1106 was more highly expressed in esophageal tumor versus normal esophagus. Gene expression was identified using standard semi-quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a semi-quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type rendered the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Applicants submit herewith the Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology (Exhibit A). This declaration was originally submitted in connection with co-pending application Serial No. 10/063,557. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

Applicants further submit that it is generally well-understood in the art that in the majority of cases, gene expression correlates with levels of protein expression. In support of Applicants' position, Applicants submit herewith the declaration of J. Christopher Grimaldi, an expert in the field of cancer biology (Exhibit B). This declaration was originally submitted in

connection with co-pending application Serial No. 10/006,867. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." The references cited in the declaration and submitted herewith support this statement.

Scientists regularly rely on the results of gene expression and even gene amplification results to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith is the declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application (Exhibit C). As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Ørntoft et al. (submitted herewith) studied transcript levels of 5600 genes in malignant bladder cancers which were linked

to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, gene amplification correspondingly increases mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene amplification influences gene expression and that gene expression influences protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1106 gene, that the PRO1106 protein is concomitantly over-expressed. Thus, Applicants submit that the PRO1106 protein and the antibodies against this protein have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed polypeptides would have diagnostic utility even if the protein were not over-expressed

Even assuming *arguendo* that, there is no correlation between gene expression and increased protein expression for PRO1106, which Applicants submit is not true, a polypeptide encoded by a gene that is over-expressed in cancer would still have a credible, specific and substantial utility. In support, Applicants submit herewith the Declaration of Avi Ashkenazi,

Ph.D., an expert in the field of cancer biology (Exhibit D). Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants submit that simultaneous testing of gene expression (or gene amplification) and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level. Even if not over-expressed, a polypeptide encoded by a gene that is over-expressed in cancer would still have utility. Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1106 polypeptides as diagnostic agents. Based on the evidence and arguments presented

herein, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, Dr. Polakis and Dr. Ashkenazi, and must treat as true the statements made by these experts. Applicant reminds the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed proteins as diagnostic agents. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the PRO1106 polypeptide set forth in the specification. In view of the above arguments, Applicants respectfully request that the PTO reconsider and withdraw the utility rejections under 35 U.S.C. §101 and §112, first paragraph.

Rejections under 35 USC §112, 2nd paragraph

The Examiner rejected Claims 1-6 and 10 as indefinite for the recitation of an "extracellular domain...lacking its associated signal peptide". The claims have been amended to recite the ECD together with its signal peptide.

Rejection under 35 U.S.C. §112, first paragraph – enablement and written description

The Examiner rejected Claims 1-5 and 12-13 under 35 U.S.C. § 112, first paragraph, as indefinite because the specification, were it enabled for an isolated polypeptide comprising SEQ ID NO:58, would still not reasonably provide enablement for a polypeptide at least 80% identical

to SEQ ID NO:58 or polypeptides that hybridize to SEQ ID NO:58. The Examiner has also rejected Claims 1-5 and 12-13 under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time of filing.

Without acquiescing to the propriety of these rejections, Applicants have amended Claims 5 and 12-13 to recite a functional recitation: "wherein the nucleic acid encoding the peptide is more highly expressed in esophageal tumors". Claims 1-4 have been cancelled without prejudice or disclaimer and hence this rejection is moot with respect to these claims. Applicants respectfully traverse this rejection to the remaining claims.

The legal standard for Enablement

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of the claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims, as amended, are enabled

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. Claims 1-4 have been cancelled. The remaining claims concern polypeptides having 99% sequence identity with the disclosed polypeptide sequence SEQ ID NO:58 and further with the functional recitation "wherein the nucleic acid encoding the polypeptide is more highly expressed in esophageal tumors." Based on the detailed description of the cloning and expression of variants of SEQ ID NO:58 in the specification, the description of the gene expression assay, the actual reduction to practice of SEQ ID NO:58 and the functional recitation in the instant claims, Applicants submit that the specification enables one skilled in the art to make the invention commensurate in scope with these claims. Further, it is known to one of skill in the art that some variation occurs naturally between individuals and that such variation can certainly be as much as 1% and may have no effect of the activity of the

protein. Further, a conservative change in the polypeptide may have no effect on the activity of the protein. Thus, variants which are 99% homologous would be known to one of skill in the art.

The legal standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d at 1563, 19 USPQ 2d at 1116(Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g. *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d at 1563, 19 USPQ 2d at 1116(Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F. 3d 989, 996 (Fed. Cir. 2000).

Arguments

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

As noted above, the present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The pending Claims are to polypeptides having 99% sequence identity with the disclosed polypeptide sequence SEQ ID NO:58 and further, "wherein the nucleic acid encoding the polypeptide is more highly expressed in esophageal tumors."

Thus, contrary to the Examiner's statements in the Office Action, the claims are not drawn to a genus of polypeptides defined only by sequence identity. Based on the detailed

description of the cloning and expression of variants of SEQ ID NO:58 in the specification, the description of the gene expression assay, the actual reduction to practice of SEQ ID NO:58 and the functional recitation in the instant claims, Applicants submit that the claimed polypeptides are adequately described.

Hence, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. §102(e)

The Examiner rejected Claims 1-4 as anticipated by U.S. Patent No. 6,573,095, issued June 2003, filed May 1999 ('095). However, Claims 1-4 have been cancelled, thus rendering the rejection moot.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 12-13 as unpatentable in view of U.S. Patent No. 6,573,095, issued June 2003, filed May 1999 ('095). According to the Examiner, the sequence set forth in the '095 patent is 97% identical to SEQ ID NO: 58. The claims are limited to isolated polypeptides having at least 99% amino acid sequence identity to SEQ ID NO: 58. In addition, Claim 12 has been amended to be dependent on Claim 5, and Claim 5 now requires that the "the nucleic acid encoding said peptide is more highly expressed in esophageal tumor than in normal esophagus."

It would not have been obvious to one of ordinary skill in the art to make the chimeric peptides as set forth in Claims 12 and 13 as amended, given the sequence taught in the '095 patent. There is no teaching or suggestion in the cited combination of references to modify the sequence set forth in the '095 patent to obtain the claimed peptides. Accordingly, withdrawal of the rejection under 35 U.S.C. § 013(a) is respectfully requested.

Conclusion

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 16, 2004

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